REMARKS

Claims 12-17, 19, and 22 will be before the Examiner. Claim 22 is new, and is supported, e.g., by page 28, section 2.4.2 of the specification.

The Examiner has rejected claims 12-15 and 19 under 35 U.S.C. § 103 over Bialer in view of Ross and French. Remaining claims 16 and 17 were rejected over these references, further in view of Thomas. Full citations have not been given as the references are all of record and cited fully in the Office Action.

Applicants have considered the Examiner's rejection and response to applicants' August 23, 2009 submission carefully, and traverse.

The Examiner's position in summary is that Bialer teaches AWD 131-138, the compound recited in the claims, as well as treatment of audiogenic clonic seizures and absence epilepsy, in genetic models of epilepsy. The Examiner concedes that the treatment of dogs is not taught by Bialer, but contends that other models do teach the treatment of dogs.

The Examiner concludes that:

> "Therefore, there would be a reasonable expectation of success that AWD 131-138 would be an effective treatment for idiopathic epilepsies."

It appears that the Examiner recognizes that "idiopathic" epilepsies are not taught by Bialer, and contends that:

> "Ross et al. teach that AGS is a form of epilepsy associated with generalized seizure displayed by clonic or tonic-clonic seizure activity" and

> "French teaches that clonic or tonic-clonic seizure activity is a form of idiopathic epilepsy."

From this, the Examiner concludes that since two references teach AGS is a form of idiopathic epilepsy:

> "(I)t would be obvious to a person of ordinary skill in the art at the time of the invention that Bialer et al. is teaching the treatment of different forms of idiopathic epilepsy with AWD 131-138. Although Bialer et al. does not teach the treatment of dogs in the AGS epilepsy model or in absence epilepsy animals, the treatment of dogs is taught in other models. Therefore, there would be a reasonable expectation of success that AWD 131-138 would be an effective treatment for idiopathic epilepsies."

As the Examiner notes, this rejection is continued from prior actions. In rebuttal, applicants have submitted declarations by Dr. med. Vet. Holger Volk and Univ.-Prof. Dr. med. Vet. Marc Vandevelde. The Examiner considered these declarations, but concluded they were unpersuasive. First, the Examiner refers to the declaration by Vandevelde, which cited and provided a paper by Löscher. Vandevelde states, at point 10 of his declaration, speaking of Löscher et al.:

> "They tested a number of commercial anticonvulsants used in humans in epileptic dogs. Contrary to their expectations the authors discovered that most available anticonvulsants, with the exception of phenobarbital and primidone, were not useful for treatment of focal and generalized seizures in dogs suffering from idiopathic epilepsy."

The Examiner concluded, in reference to this passage:

> "Applicants present arguments by way of Declarations by Vandevelde and Volk. In particular, Vandevelde is of the opinion that the use of AWD 131-138 for the treatment of idiopathic epilepsy in dogs was not obvious at the time the

subject patent application was filed. Vandevelde argues that the animal models of electrical induction seizures, chemical induction of seizures and audiogenic seizures are not models that provide a suggestion that a compound is used as an anticonvulsant in idiopathic epilepsy in dogs. It is discussed that drugs with rapid metabolism and rapid elimination are not successful anticonvulsants in man because idiopathic seizures can occur at any time. Vandevelde discusses that drugs which are useful for treatment of human epilepsy are in most cases not useful for the treatment of canine epilepsy.

Vandevelde points to a paper by Loscher et al. in view a review of available anticonvulsants tested that are useful in humans were found not be useful in dogs in idiopathic epilepsy. Vandevelde also points to a paper by Rostock in which it is argued that data from experimental animal models are of limited relevance for the treatment of canine epilepsy. Vandevelde discusses that canines metabolize chemicals very quickly, resulting in short half lives and low plasma levels and experimental animal data or data generated in human patients can be extrapolated to epileptic dogs for this reasons.

In response to the above arguments concerning the Loscher reference, it is noted that the reference discusses that previous studies suggest that epilepsy in dogs closely approximates that disease in man (see first paragraph of Discussion). Further, Loscher concludes that the data of that particular article supplied by Applicants indicate that the epileptic dog is indeed a suitable model of human epilepsy. Further, Loscher found parallels betweens one of the antiepileptics tested, for instance, the efficacy of primidone in dogs corresponds to with that in humans (see fourth paragraph in Discussion). This refutes the argument that definitions of human epilepsy cannot be extrapolated to dogs because the Loscher article presented by Applicants shows a clear parallel with a lot of anticonvulsants available at that time."

The Examiner's statement that "Löscher concludes that the data of that particular article supplied by applicants indicate that the epileptic dog is indeed a suitable model of human epilepsy."

This misstates Löscher's conclusion. The "Summary" of the articles ends with the statement"

> "The model provides special advantages for the study of efficacy of chronic antiepileptic drug treatment, provided the pharmacokinetics of the drug to be studies allows the maintenance of effective drug levels."

(emphasis added).

The declarations provided established clearly that the pharmacokinetics of the standard drugs do not, as a rule, permit maintenance of effective drug levels in the dog.

Löscher's summary found efficacy with phenobarbital and primidone. Not found to be effective were phenytoin, carbamazepine, valproic acid, diazepam, clonazepam, and nitrazepam. Hence, the Examiner's statement that a clear parallel with "a lot of anticonvulsants available at the time" is questioned. Six were ineffective, two were effective. This hardly counts as "a lot" of parallels.

Dr. Löscher himself has provided a declaration, and a copy is appended hereto.

Dr. Löscher agrees that the diseases canine epilepsy and human epilepsy show similarities; however, these similarities are outweighed by the differences, enumerated at paragraphs 5 of his declaration.

Dr. Löscher elaborates on the differences in efficacy of the drugs he and his colleagues tested, at paragraph 8 of his declaration. Indeed, Löscher states that his own

group has failed to establish the epileptic dog as a model for human epilepsy. See paragraph 9 of the Löscher declaration.

It is submitted that the Examiner's conclusions regarding the Löscher paper are refuted by the lead author of the paper himself. Thus, the Vandevelde declaration must be reassessed, together with the newly submitted Löscher declaration. When it is, it is submitted that the Examiner's conclusions regarding the declarations and the paper, will be seen to be unsupportable.

Applicants have provided substantial evidence that there are fundamental differences in the animal models used for studying epilepsy. These differences are attributable to the animals themselves, not to any parameter that the investigator can control.

For example, applicants have shown that dogs metabolize drugs in a manner quite distinct from that of humans and rodents. They point, again, to the fact that dogs, due to their carnivorous diet possess a short gut and due to their high metabolic activity exhibit a very different rate of turnover of small molecules circulating in their blood.

It is submitted, thus, that the only type of therapeutic agent which could be assumed effective in dogs, is one possessing appropriate pharmacokinetic properties. Such properties, however, are not predictable. Neither molecular structure, nor results in other species provide evidence to support this conclusion. The Löscher paper, which is of record, provides a comparison of pharmacokinetic properties in dogs and humans, at Table 3 (page 84). As just one example, valproic acid has a half-life of 8-15 hours in humans. In dogs, it is 0.8 – 2.7 hours. The results for diazepam are perhaps more striking, with a half-life of 24-72 hours for humans, and 1-5 hours for dogs.

Indeed, Löscher concluded as quoted supra, and Vandenvelde's conclusions must be taken as persuasive.

It is understood that references cited by the Examiner also deal with testing in rodent models. Applicants have argued non-applicability of these models as well. At page 3 of the last Office Action, however, the Examiner states:

> "Regarding the arguments concerning the Rostock reference supplied by Applicants that data shows that data from experimental animals are of limited relevance in the treatment of canine epilepsy, it is unclear how this reference makes this point."

In response, applicants elaborate on the Vandenvelde declaration which discusses this reference.

As Vandenvelde explains, Rostock discusses phenytoin, carbamazepine, and valproic acid. These compounds, the so-called "mainstays of old generation epileptics for treatment of humans," are also so noted by French, cited by the Examiner. Also discussed in Rostock are phenobarbital and "D-23129".

Rostock used, as animal models, mice and rats, with electrically induced seizures ("MES"), chemically induced seizures (PTZ, picrotoxin, and NMDA), motor impaired mice and rats, and genetically modified mice. All animals showed forms of induced epilepsy.

Table 1-4 of Rostock summarize experiments, and conclude:

> "We expect that D-23129 will improve the treatment of refractory seizures in humans."

Rostock is clearly trying to establish an extrapolation between what is efficacious in rodent models and humans. No mention is made as to dogs and in fact, as was detailed

supra Löscher shows, in Table 3 in particular, that the "mainstays" for treatment of humans, e.g., phenytain, carbamazepine and valproic acid, were not effective in dogs.

Hence, what the declaration is stating, and as supported by the art is that to the degree one may extrapolate between rodent models and humans, such extrapolations cannot be carried over to dogs. The evidence simply does not support it.

The Examiner also appears to be of the position that the murine models disclosed in the applied references suggest a reasonable expectation of success in dogs. Applicants submit that this is not the case.

The claimed subject matter relates to idiopathic epilepsy. The references, as well as the prosecution, supports an interpretation of "idiopathic" epilepsy, which distinguishes it from the induced epilepsy rodent models relied upon by the Examiner. The Löscher declaration, moreover, establishes that such models, while resembling human epilepsy, are not applicable for idiopathic epilepsy in dogs. Please note page 3 of the Löscher declaration and the discussion of the Licht reference, provided therewith. Löscher establishes that one of ordinary skill in the art would not select a drug useful in petit-mal seizures, because these are not found in dogs. Rather, one would look for a drug effective on tonic-clonic convulsions, and such are not disclosed or suggested by the cited references.

The Examiner has maintained her prior rejection as a whole, i.e., Bialer plus Ross plus French. This position is believed to remain untenable, as explained herein.

As has been pointed out previously, Bialer tested drugs, in rodent models, for potential applicability to humans. As has been shown by the previously submitted declaration of Vandenvelde and Volk, and now by Löscher, the use of a murine model provides no suggestion of efficacy in dogs. The evidence simply does not support it. As

a practical matter, most of the drugs which have proven to be effective in rodent models, and in humans, did not work in dogs. The unique physiology of the dog suggests that the pharmacokinetics of any drug which would be effective in dogs would have to be different from those effective in rodents and humans. Yet further, the rodent models, dealing as they do with induced epilepsy, do not correlate to idiopathic epilepsy.

The Examiner appears to take the position that the WAG model disclosed in Bialer is representative of idiopathic epilepsy. Such is not the case.

WAG epilepsy, as has been shown, is a form of genetically linked epilepsy. By definition, it is not and cannot be idiopathic. Furthermore, the Bialer reference explains quite clearly, at page 12, right column, last paragraph, that the WAG rat is a model for absence epilepsy. WAG rats, as is typical of absence epilepsy, exhibit petit-mal seizures, or absence episodes. The evidence as discussion by Löscher in his declaration, shows that dogs do not exhibit these symptoms.

The Examiner attempts to combine Bialer with Ross and French, but the combination is attenuated at best. French discusses symptoms associated with "idiopathic generalized epilepsy syndromes," as seen in humans. In contrast, as Löscher has explained, at paragraph 5 of his declaration the seizure pattern observed in dogs is very specific and not at all similar to humans.

The Ross paper, as has been explained previously, discusses induced epilepsy in rodents. Given the teachings of the art as to inapplicability of rodent models to dogs, as well as the inapplicability of data on induced epilepsy to idiopathic epilepsy, it is submitted that the references taken together fail to establish a prima facie case of obviousness. Assuming arguendo that they do, the combined declarations and references provided in support thereof rebut any such case.

Withdrawal of the rejection is believed proper and is urged.

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Applicant is hereby authorized to charge the extension fee to the credit card. PTO Form 2038 is enclosed. The Commissioner is hereby authorized to deduct any additional fees due with this response from our Deposit Account No. 50-0624, under Order No. NY-HUBR 1230-US (10312533) the undersigned is authorized to draw.

Dated: March 19, 2010

Respectfully submitted,

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Attachment: Löscher Declaration
Petition for Extension of Time (2-months)